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Gene Variants and Epigenetics That Lead to Gender Dysphoria

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ABSTRACT: These days, the rate of gender dysphoria among transgender individuals has increased drastically. Gender dysphoria is a significant issue affecting every aspect of individuals' daily activities. It induces significant stress and might eventually cause an impairment. Historically, the etiology of gender dysphoria solely focused on the anatomical aspect, mentioning that men's and women's brains are distinct. However, it is now believed to be multifactorial, and emerging researchers are trying to shed light on both brain structures and genes that might contribute to gender dysphoria. To explore the possible etiologies of gender dysphoria, this paper reviews the evidence of how epigenetics contributes to gender dysphoria. The basis includes the role of sex-determining genes, anatomical differences among various populations, epigenetics, and mutation of the RYR3 gene. Epigenetics focuses solely on CpGs methylation. Thus far, these mechanisms could not wholly explain the exact mechanism causing gender dysphoria; therefore, additional research is required to disclose this information. Ultimately, understanding the mechanism of gender dysphoria will promote a better quality of life for individuals experiencing gender dysphoria.

KEYWORDS: Epigenetics, Gender dysphoria, Neurostimulation Differences, RYR3, Sexual Differentiation.

INTRODUCTION

Transgender has been an increasing trend over the past few years [1, 2]. Nevertheless, there is still little knowledge about transgender, whether it be anatomy, clinical pharmacology, or even treatments [3]. One of the most concerning issues among transgender is Gender dysphoria [4, 5]. The past prevalence for gender dysphoria was considered uncommon, however, it has increased approximately, 1 in 10,000 adult males and 1 in 30,000 adult females in the past decades [1]. Diagnostic and Statistical Manual of Mental disorders defines *gender dysphoria* as a "marked incongruence between their experienced or expressed gender and the one they were assigned at birth" [1, 6].

According to the International Classification of Diseases ICD-11, gender incongruence (GI) is an incongruence between the individual's assigned sex and their experiences of gender [7, 8]. Individuals with gender incongruence who experience difficulties or significant burdens might develop gender dysphoria [7, 9]. With a better understanding, gender incongruence is no longer related to a mental health condition [10]. However, there are still people experiencing this gender incongruence and eventually develop gender dysphoria, which is an unease feeling individuals might have due to gender incongruence [3].

The etiology of gender dysphoria is unclear but is trusted to be multifactorial, holding many factors together, including both psychological and biological factors [11, 12]. In these recent days, biological factors have become an interesting topic when speaking about gender dysphoria; it includes hormonal and genetic factors which are linked together, having effects on the brain, the location believed to be the one determining gender identity [11-13]. It is known that there are region-specific dimorphisms in the brain, with some structures larger in females and some larger in males. Nevertheless, there is still no evidence to prove that these dimorphisms impact or influence the development of gender dysphoria [2]. Investigating heritability might enhance the demonstration of the genetic factor for developing gender dysphoria [2, 14]. The purpose of this review is to have a better understanding of the etiology of gender dysphoria which will lead to better support for individuals who experience this, or even better, prevent this from happening.

A. Sex-Determining Genes of the Human Brain

There are studies showing that the anatomical structures of females and males brain are different in both structural and hormonal aspects, and in this review, the focus will be on the hormonal and genetic aspects [15]. There is hypothesis mentioning that individuals who experience gender incongruence have a brain structure resembling the sex that they are discerned to be [5]. It is still debatable whether gender dysphoria is developed due to thought patterns that influence the brain anatomy or whether it is the anatomy of the brain itself [9, 15].

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Three weeks after fertilization, the fetus' brain begins to form. This process occurs during the second trimester of pregnancy, developing the central part of the central nervous system [5, 16]. Steroid hormones play an important role in gonadal development and eventually bring out the effect on brain's sexual development [17]. This will lead to a change in sizes of several regions in the brain, quantity of neurotransmitters, and numbers of nerve cells [5, 12].

B. Differences of Neurostimulation and Anatomical in Cisgender Adults

Cisgender individuals are those who have matched assigned sex and gender identity [2]. The origin of male brain sexual differentiation is believed to begin during the gestation and the perinatal period which two peaks of gonadal hormones are seen and when it comes to puberty, sex hormones will then affect the prior established neuronal patterns [18, 19]. Commonly, males have a higher mean volume in the hippocampus which involved in spatial memory and consolidating information from short-term and long-term memory, the amygdala, where emotions are processed, and the thalamus, which relays motor and sensory signals [14, 20]. Moreover, there are higher androgen receptors compared to estrogen receptors in males, whereas females have larger hippocampus with higher estrogen hormones but lower in androgen receptors [12, 21]. There are recent studies show that averagely, men's brains are 8-13% larger than women, confirming that men have larger total brain volume, cerebrum and cerebellum [21, 22]. On the other hand, women have higher density in the left frontal lobe and larger volumes in the right frontal lobe [2]. Eventually, these results confirm that the brain develops asymmetrically, confirming the anatomical differences between males and females [18]. Nonetheless, individuals experiencing gender dysphoria should not be restrictedly scaled to only males and females, but rather be scaled on the middle ground [18]. Therefore, it could be hypothesized that hormonal imbalance might play some roles in individuals developing gender dysphoria [2]. Furthermore, environmental factors are another important factors that might alter the brain function [12].

C. Epigenetics as a Basis of Gender Incongruence

DNA methylation is considered one of the epigenetics marks and is known to be inherited through cell divisions. It does not alter DNA sequence [11, 23]. However, it changes how genes are being expressed, eventually affecting how genes can function and their activities [23]. Due to its ability to establish phenotypes, it is believed to be part of the gender incongruence etiologies. A study prior to gender-affirming hormone treatment (GAHT) showed that cis and trans populations exhibited different global CpG methylation profiles [11, 23]. The PCA analysis revealed that the spatial representation of these groups' global methylation differed significantly [23]. When comparing people designated as male at birth (cis men versus trans women), CpGs with substantial methylation were identified in islands [11, 24]. However, compared to females assigned at birth, only two CpGs exhibited significant methylation alterations; none were detected in islands [24]. In addition, one of these CpGs, associated with the MPPED2 gene, is shared by both trans males and trans women [11, 24]. At least four of these genes are engaged in brain development and neurogenesis among the CpGs with the highest statistical significance. The following genes are involved: SLC6A20, PLEKHA5, NHLH1, and MPPED2 [11]. Overall, the findings imply that these genes may play a role in brain development and that epigenetic variables play a role in a developmental differential associated with gender incongruence [11].

In comparing cis men and trans women, CpGs passed statistical correction (FDR p 0.05; fold change 2), including 22 CpGs placed on islands; 14 were hypomethylated, and 8 were hypermethylated in the cis population [11]. This study examined CpG islands because they frequently correspond with promoter regions and can alter gene expression [11]. In trans women, the most significant CpGs were associated with the genes WDR45B, SLC6A20, NHLH1, PLEKHA5, UBALD1, SLC37A1, ARL6IP1, GRASP, NCOA6, ABT1, and C17orf79 [11]. At least four of the most statistically significant CpGs were engaged in brain development and neurogenesis (WDR45B, SLC6A20, NHLH1, and PLEKHA5), and three were associated with transcriptional functions (NHLH1, NCOA6, and ABT1) [25]. In addition, the gene C17orf79 is associated with chromatin organisation, and its activation increases AR transcription [11]. Two more genes were associated with glutamate synapses (ARL6IP1 and GRASP) [11]. WDR45B is a component of the autophagy machinery that regulates the primary intracellular degradation process in which cytoplasmic components are bundled into autophagosomes and transported to lysosomes for breakdown [11]. Experiments using knockout (KO) mice reveal numerous enlarged axons and cerebellum atrophy [11]. In contrast, the gene SLC6A20 synthesises an amino acid transporter called proline and regulates glycine levels in the brain [11]. Recent investigations have shown that this gene is highly expressed in a variety of brain areas, as well as in astrocytes and microglia, but to a lesser extent in glutamate and GABAergic

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neurons [26, 27]. This may indicate that SLC6A20 proteins in the brain regulate both proline and glycine homeostasis [11]. The NHLH1 gene is involved in neurogenesis and encodes a helix-loop-helix (HLH) protein that is a member of a family of transcription factors, some of which have been found to play a significant role in the growth and development of a wide range of issues [11, 28]. This protein is predominantly expressed in the cerebellum of the brain [11, 28]. NHLH1 is a neuronal marker [28]. Its function may be to regulate the expression of specific neuronal genes at the level of the initial neurons, thereby establishing the initial axon scaffold tracts [11, 28]. This gene might play a significant role in the development of the mouse brain [11, 28]. However, it was related to IL-8 secretion and NF-kappaB signalling [11]. In contrast, PLEKHA5 is associated with cell migration and cell-to-cell contacts and may also serve as a modulator of the brain homing phenotype [29-31].

Regarding gene NCOA6, the protein produced by this gene is a transcriptional coactivator that can increase the transcriptional activator actions of nuclear hormone receptors [32, 33]. It is a nuclear receptor coactivator that binds directly to nuclear receptors for steroids (glucocorticoid receptors GR and ERs) and increases hormone-dependent transcriptional activity [32]. This gene's associated Gene Ontology annotations include chromatin binding and transcription coactivator activity [11, 32]. In addition, earlier DNA studies of SRC-1 and SRC-2 coactivator polymorphisms have suggested their alleged role in the process of brain dimorphism [7, 8]. In addition, mouse studies reveal that the protein produced by the gene ABT1 activates basal transcription from class II promoters by interacting with the DNA of class II promoters [11]. The GO annotations associated with this gene are transcription coactivator activity, DNA binding, RNA binding, control of transcription by RNA polymerase II, and transcription coactivator activity [8, 34]. In contrast, when comparing cis women to trans men, significant methylation appeared in only two CpGs, neither of which were islands [35, 36]. The Venn analysis revealed that both trans groups share one of the critical CpGs. Thus, the MPPED2 (Metallophosphoesterase Domain Containing 2) gene's cg23944405 exhibited statistically significant variations in methylation among trans males and trans women [11]. This gene is expressed in most human tissues, including the brain, in both cis men and women and is mainly expressed in foetal brains [37]. In addition, there was a scholar characterised MPPED2 expression in human tissues of neuronal origin and demonstrated that MPPED2 expression is modulated during development, attributing to this gene a crucial role in the embryonic processes of neuronal differentiation that occur during CNS development [37]. In addition, this gene has been linked to increased inflammation and adverse clinical outcomes following severe physical trauma [24]. Moreover, the functional significance of MPPED2 regulation is linked to cell cycle inhibition as it drives neural precursor apoptosis and differentiation [24]. The MPPED2 gene-related Cg23944405 is hypermethylated in both trans populations [7]. However, this CpG is not located on an island, it is unable to conclude that the hypermethylation in the transgender group was associated with a low gene expression level. Nonetheless, research suggests that low metallophosphoesterase activity (*in vitro*) may play a role in CNS development [38].

D. Mutation of Ryanodine Receptor 3 and Gender Dysphoria

Another hypothesis that is related to gender dysphoria is gene mutation. A research applied next generation sequencing technique and discovered heterozygous mutations of RYR3 in transgender individuals [27]. It is found that RYR3, a ryanodine receptor, which releases calcium from intracellular storage, is recurrently mutated in three female-to-male transgender individuals, and none were found in the control group [37]. Further analysis revealed that most mutated genes are involved in ion transportation [37]. The ion transport-related module components in the female-to-male transgenders network included eleven following proteins: ITPR1, ITPR2, ITPR3, RYR2, RYR3, NNT, CACNB2, CTT1B, CPT2, PSEN2, and PLCG2 [37]. The ion transport-related module components in the male-to-male transgenders network included the following seven proteins: ITPR3, TRPM5, KCNB1, ATP2B2, CACNA1I, XCR1, and PLCG2 [37]. When examining ion transport-related module components expression, RYR3 is found to be expressed strongly in the associative striatum, hippocampus, frontal lobe, and caudate nucleus but yields medium to low signals in other regions [24]. Nevertheless, both ITPR3 and PLCG2 were expressed consistently in each brain region [24]. To probe into structural templates, this research identified the protein sequence of Homo sapiens RYR3 and formed its 3D structures [24]. The result affirmed that there were mutations occurring, introducing new intramolecular hydrogen bonds, eventually causing changes in molecular structures [37]. The mutations mentioned above involved three homology models, which are manual mutations of p. 2A>T, p. 1518R>H, and p. 2847T>A. The mutation significantly yields a structural change in RYR3 protein is p. 1518R>H. Three intramolecular hydrogen bonds were formed between Met819, Gly1520, Trp1521, and His1518, influencing structural change that shifted the side chain of the His1518 from outside to inside, which contrasts with the wild-type RYR3 model [37]. In particular,

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Arg1518 in wild type showed no interactions with the mentioned residues, which also applied in the p. 2A>T and p. 2847T>A mutants [24, 37]. On the contrary, p. 2A>T mutant and the wild type exhibited hydrogen bond formation between residue Ala2 and Thr2 with Met1 instead [39]. Surprisingly, the side chains of these two residues shared similar lengths [40]. In both p. 2847T>A mutant and wild type, a hydrogen bond is still found related to Ala and Thr, however, it also includes a bond between Ala and Ser; which can either be between Thr2847 and Ser2850 or Ala2847 and Ser2850 [40]. The structural changes in p. 2A>T and p. 2847T>A mutants are per se not as obvious as others [40, 41].

This research shows that close functional coordination between ion transporters and plasmalemmal ion channels is essential for neurons' electrical activity [42]. Mutation of RYR3 can cause an imbalance in intracellular calcium homeostasis leading to impairment of neuronal function [37]. Even though, the susceptibility of gender dysphoria from RYR3 mutation is considered equal among individuals, the risk increase might be related to the number of variants within each individuals [37]. It is thought that gender dysphoria is a consequence of atypical cerebral sexual differentiation; however, it is now known that multiple structures and networks are involved instead of a single area [24, 27]. This indicates that sex hormones play an important role in sexual differentiation of the brain, which can be concluded that hormonal and genetics deviations might cause a discrepancy between the sexual brain and genital differentiation, and eventually leads to gender dysphoria [22, 43].

E. Future Research

Genetics appears to be the foundation of gender dysphoria. Nevertheless, genetics alone cannot fully explain the incidence or etiology of gender dysphoria [15]. Although there appears to be a degree of genetic underpinning, multifactorial factors, such as social upbringing and access to education, are believed to play an important role in causing gender dysphoria [27]. The psychological aspect is considered to be another important part of sexual differentiation. How children are being raised and interaction between family members may alter the brain's development, more importantly, affecting how children perceive themselves [5]. Another concerning issue is the effects of sexual identity on neural function [4, 19]. Even though the study of the mutation of RYR3 gene reveals a valuable information of how neurons' electrical activity may affect neuronal function, it is still inadequate to understand the definite etiology of gender dysphoria. Besides the aspect of neuroanatomy, the disorders among men and women vary as well. For instance, the differences in the incidence of psychiatric disorders between men and women [1]. Little research has been conducted on transgender individuals and how their brain structures differ from those whose sex and gender are compatible [44]. [9, 46]. For instance, the number of women diagnosed with Alzheimer's exceeds that of men [9, 47]. In light of this, it is crucial to comprehend the biochemistry of the brain that explains why the risk is elevated in both sexes Further investigation into this sector could shed light on the genesis of gender dysphoria and how it impacts brain function [2, 39]. More research must be conducted in order to go beyond the observed neuroanatomy of the brain, enhances the understanding of how the brains of people with gender dysphoria correlate with those whose sex and gender are matched, while also shedding light on the influence of society on the behaviour of people with gender dysphoria [45]. With a better understanding of the condition, transgender individuals may receive greater assistance and awareness, reducing the suffering associated with gender dysphoria [12, 15, 26].

F. Conclusion

Several studies and research were undertaken to affirm that masculinisation or feminisation of the gonads does not always coincide with the growth and function of the brain. These studies are able to explicate the contrast between individuals' assigned sex and gender. However, it is acknowledged that the definite mechanism of gender dysphoria is still unknown, although the significance of genetic and hormonal factors is evident. Numerous investigations have revealed two distinct global CpG methylation profiles in cis and trans people prior to GAHT. These epigenetic modifications to DNA are associated with many genes involved in critical developmental pathways. In addition, the methylation data, in conjunction with the earlier genetic data, supports the concept that gender incongruence is a complex multifactorial trait involving intricate interactions between sex hormones, sex steroid receptors, genetics, and epigenetics. Mutation of RYR3 gene also shares interesting information among transgender individuals and cisgenders individuals. This mutation supports that RYR3 mutation causes an imbalance in calcium homeostasis, altering neuronal function. This lends credence to the notion that parallel integrating genetic and epigenetic techniques may be an effective strategy for comprehending the mechanisms behind brain dimorphism. However, additional research is required to uncover gender dysphoria's exact mechanism and investigate its inheritance pattern. Ultimately, conducting more research will give a better understanding of

the condition and helps increase awareness among the population, resulting in better quality of life and acceptance for individuals who experience gender dysphoria.

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